REMARKS

Applicant has amended the specification to claim priority from PCT/US00/01044, filed on January 14, 2000 which claims priority from U.S. Patent Application No. 60/116,168, filed on January 15, 1999.

Applicant has also amended the specification by replacing the paragraph beginning with the sentence "Figure 1 shows a sequence alignment of soluble recombinant murine and human TWEAK proteins." on pages 5, line 32-33 with the substitute paragraph "**Figure 1** shows a sequence alignment of soluble recombinant murine (SEQ ID NO. 1) and human (SEQ ID NO. 2) TWEAK proteins. Identical residues are indicated in bold face."

Applicant has cancelled claims 2-3 and 10-11 without prejudice and reserves the right to prosecute the subject matter of the cancelled claims in any future application claiming benefit or priority herefrom under 35 U.S.C. § 120.

Applicant acknowledges with appreciation the Examiner's reconsideration in extending the species search to also cover organ transplant failure resulting from graft rejection. In view of the Examiner's statement, applicant has amended claim 1 to recite a method for blocking the development or treating or reducing the severity or effects of a Graft-Versus-Host Disease or an organ transplant failure resulting from graft rejection in an animal comprising the step of administering a pharmaceutical composition which comprises a therapeutically effective amount of an anti-TWEAK polypeptide monoclonal antibody and a pharmaceutically acceptable carrier. Support for this amendment may be found, *e.g.*, at page 5, lines 13-16 and lines 23-25; page 9, lines 6-10; page 12, line 25-page 13, line 32; page 17, lines 9-12; Example 2 on page 19; and Figure 4 of the specification.

Claim 4 has been amended to delete the dependency from cancelled claim 2.

Claim 12, which depends from claim 1, has been amended to recite that the Graft-Versus-Host Disease or organ transplant failure is caused by a Th1 cell-mediated immune response. Claim 13, which depends from claim 1, has been amended to recite that the Graft-Versus-Host Disease or organ transplant failure is caused by a Th2 cell-mediated immune response. Claim 14, which depends from claim 1, has been amended to recite that the Graft-Versus-Host Disease or organ transplant failure is caused by a combination of a Th1 and a Th2 cell-mediated immune response. Support for amended claims 12-14 can be found, *e.g.*, at page 4, line 17-page 5, line 5; page 12, line 25-page 13, line 32; and page 15, lines 24-37.

Applicant has added claim 23 to recite a method according to claim 1, wherein said anti-TWEAK polypeptide monoclonal antibody is selected from the group consisting of: (a) a chimeric antibody, (b) a humanized antibody, and (c) a recombinant antibody. Support for claim 23 may be found, *e.g.*, at page 11, line 14-page 12, line 22 of the specification.

The amendments and new claim presented herein do not constitute new matter. In sum, claims 1, 4-5, 12-14 and 23 are pending.

THE OBJECTIONS

The Examiner has objected to the specification under 37 C.F.R. § 1.821(d) for failing to provide a sequence identifier for each individual sequence. The Examiner points specifically to Figure 1 on page 5, line 32, which recites two TWEAK sequences (murine and human) that the Examiner contends must each have a sequence identifier. Applicant has amended

the specification to insert sequence identifiers on page 5. Thus, the Examiner's objection has been obviated and applicant requests withdrawal thereof.

The Examiner acknowledges applicant's claim for priority based on PCT/US00/01044, filed on January 14, 2000 but notes that "applicant has not filed a certified copy of the PCT/US00/01044 application as required by 35 U.S.C. § 119(b)." Applicant believes that the Examiner meant that priority is claimed under 35 U.S.C. § 365(b). Consistent with the requirements for claiming priority to a PCT application, applicant stands ready to file a certified copy of PCT/US00/01044 upon receipt of same from the WIPO.

THE REJECTIONS

ENABLEMENT

Claims 1-5 and 10-14 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking enablement. The Examiner contends that the specification does not enable for:

(1) a method for blocking the development or treating or reducing the severity or effects of any immunological disorders in an animal comprising the step of administering any pharmaceutical composition which comprises a therapeutically effective amount of any TWEAK blocking agent and a pharmaceutically acceptable carrier in claim 1;

(2) a method for inhibiting any immune response in an animal comprising the step of administering any pharmaceutical composition which comprises an effective amount of any TWEAK blocking agent and a pharmaceutically effective carrier in claim 2;

(3) methods wherein the TWEAK blocking agent is any antibody directed against the TWEAK ligand in

claim 3(a); any monoclonal antibody directed against the TWEAK surface ligand in claim 10; or the antibody is directed against any subunit of the TWEAK ligand in claim 11;

(4) methods wherein the immune response is any Th1 cell-mediated immune response in claim 12; any Th2 cell-mediated immune response in claim 13 or any Th1 and any Th2 cell-mediated response in claim 14.

To the extent that the Examiner views the specification as enabling a method of blocking the development or treating or reducing the severity or effects in a subject having a Graft-versus-Host disease and organ transplant failure resulting from graft rejection comprising administering an anti-TWEAK ligand monoclonal antibody, applicant agrees and states that, at a minimum, amended claim 1 and the claims dependent therefrom (claims 4-5 and 12-14) are enabled.

The Examiner alleges that "the current state of the art in antibody therapeutics and the predictability of treatment efficacy is complicated by the potential for antibody interactions with irrelevant or [competing, *sic*] epitopes." Applicant disagrees. The Examiner relies on Ward et al., which discusses various methods of blocking adhesion molecules, to support this proposition. However, *Ward* states that "[M]onoclonal antibodies with blocking activities for various adhesion molecules represent the *most common approach* to date for interfering with development of the inflammatory response." *See, Ward et al.*, Therapeutic Immunology 1, pp. 165-171 (1994) at p. 167 (emphasis added). Thus, in contrast to the Examiner's assertion, *Ward* does not teach that using blocking antibodies for therapeutic purposes is unpredictable, but rather, that it is the most common approach in the art for disrupting protein-protein interactions.

The Examiner alleges that "[O]ne skilled in the art at the time of the invention would not be able to predict which compounds such as antibodies will block immunological disorders or inhibit the immune response." Applicant disagrees. The instant application teaches for the first time that antibodies may be used *in vivo* to block the development or treat or reduce the severity or effects of a Graft-Versus-Host Disease or an organ transplant failure resulting from graft rejection.

The art of monoclonal antibody production has been held to be not unpredictable. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). In *In re Wands*, the issue on appeal was whether the specification enables one skilled in the art to make high-affinity IgM anti-HbsAg monoclonal antibodies without undue experimentation. *Id.* at 735. The Court held that "it would not require undue experimentation to obtain antibodies needed to practice the claimed invention." *Id.* at 740. Thus, a person of skill in the art, based on the teachings of the instant application at the time of filing, would be able to generate many lines of anti-TWEAK polypeptide monoclonal antibodies.

Furthermore, the therapeutic use of antibodies has been used for decades. *See, e.g.*, Abbas, A.K., Lichtman, A.H. and Pober, J.S. (Eds.) General Properties of Immune Responses, Ch. 1, pp. 4-12; Immunity to Microbes, Ch. 15, pp. 302-316, In Cellular and Molecular Immunology, Philadelphia: W.B. Saunders Company, 1991, attached hereto as Exhibit B. A person of skill in the art would be able to follow the teachings of the instant application and identify which of the many lines of monoclonal antibodies has a therapeutic effect in animal models of Graft-Versus-Host Disease or organ transplant

failure. For at least these reasons, claims 1, 4-5 and 12-14 are fully enabled by the instant specification.

Claim 1, as amended, recites a method for blocking the development or treating or reducing the severity or effects of a Graft-Versus-Host Disease or an organ transplant failure resulting from graft rejection in an animal comprising the step of administering a pharmaceutical composition which comprises a therapeutically effective amount of an anti-TWEAK polypeptide monoclonal antibody and a pharmaceutically acceptable carrier. Because the Examiner's rejection has been obviated, applicant requests withdrawal of this rejection.

Claims 4, 5 and 12-14, which depend from amended claim 1, are also enabled. Claim 4, which depends from claim 1, has been amended to delete the dependency from cancelled claim 2, and recites that the animal is mammalian. Claim 5, which depends from claim 4, recites that the mammal is human.

Claim 12, which depends from claim 1, has been amended to recite that the Graft-versus-Host Disease or organ transplant failure is caused by a Th1 cell-mediated immune response. Claim 13, which depends from claim 1, has been amended to recite that the Graft-versus-Host Disease or organ transplant failure is caused by a Th2 cell-mediated immune response. Claim 14, which depends from claim 1, has been amended to recite that the Graft-versus-Host Disease or organ transplant failure is caused by a combination of a Th1 cell-mediated and a Th2 cell-mediated immune response.

Based on the teachings of the instant application, a person of skill in the art at the time of filing, having in hand the anti-TWEAK polypeptide monoclonal antibodies described therein, would immediately recognize that the monoclonal antibodies could be used to treat Graft-versus-Host

Disease caused by a Th1 or Th2 cell-mediated immune response. *See*, Krenger and Ferrara, *Immunol. Res.* 15:50-73 (1996), attached hereto as Exhibit C.

Krenger and Ferrara describe the development of acute Graft-versus-Host Disease as a three-step process. Specifically, donor T cell activation during the second step of Graft-versus-Host Disease pathophysiology is characterized by proliferation of type 1 T cells and secretion of IL-2 and IFN-γ. *Id.* at figure 2 on page 55 and page 56, column 1, lines 1-8 and lines 25-28. Moreover, *Krenger and Ferrara* describe that "distinct immunological patterns observed in two murine models of acute and chronic Graft-versus-Host Disease are [also] associated with differential activation of type 1 and type 2 T cell subsets after allogeneic [Bone Marrow Transplants]." *Krenger and Ferrara* also describe that a classical lethal acute Graft-versus-Host Disease syndrome is linked to the preferential activation of donor T cells secreting IL-2 and IFN-γ while the less severe chronic form of Graft-versus-Host Disease is characterized a type 2 cytokine response where IL-4 and IL-10 are preferentially produced. *Id.* at page 61, column 2, lines 29-33 and 38-43, page 62, column 1, lines 2-10.

Similarly, based on the teachings of the instant application, a person of skill in the art at the time of filing, having in hand the anti-TWEAK polypeptide monoclonal antibodies described therein, would immediately recognize that the monoclonal antibodies could be used to treat organ transplant failure caused by a Th1 or Th2 cell-mediated immune response. *See*, Dallman, *Curr Opin Immunol* 7(5):632-38 (1995), attached hereto as Exhibit D. *Dallman* states that "acute graft rejection is driven either by the Th0 cell, which is capable of expressing many different cytokines, or by a

mixture of differentiated Th1 and Th2 cells." *Id.* at page 632, column 2, lines 2-6.

For at least the reasons stated, instant claims 1, 4-5 and 12-14 are fully enabled and the Examiner's rejection has been obviated. Applicant requests withdrawal of this rejection.

The rejection of claims 2-3 and 10-11 has been rendered moot by their cancellation herein.

WRITTEN DESCRIPTION

Claims 1-5 and 10-14 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time of filing, had possession of the claimed invention. Specifically, the Examiner asserts that the applicant was not in possession of:

(1) any method for blocking the development or treating or reducing the severity or effects of any immunological disorders in an animal comprising the step of administering any pharmaceutical composition which comprises a therapeutically effective amount of any TWEAK blocking agent and a pharmaceutical acceptable carrier in claim 1;

(2) a method for inhibiting any immune response in an animal comprising the step of administering any pharmaceutical composition which comprises an effective amount of any TWEAK blocking agent and a pharmaceutically effective carrier in claims 2;

(3) methods wherein the TWEAK blocking agent is any antibody directed against the TWEAK ligand in claim 3(a); any monoclonal antibody directed against the TWEAK surface ligand in claim 10; or the antibody is directed against any subunit

of the TWEAK ligand in claim 11;

(4) methods wherein the immune response is any Th1 cell-mediated immune response in claim 12; any Th2 cell-mediated immune response in claim 13 or any Th1 and any Th2 cell-mediated response in claim 14.

To the extent that in the Examiner's opinion, applicant is in possession of a method for blocking the development or treating or reducing the severity or effects in a subject having a Graft-versus-Host disease and organ transplant failure resulting from graft rejection comprising administering an anti-TWEAK ligand monoclonal antibody, applicant agrees and states that as amended, claim 1 and the claims dependent therefrom (claims 4-5 and 12-14) are supported by ample written description in the specification.

As discussed above, amended claim 1 recites a method for blocking the development or treating or reducing the severity or effects of a Graft-Versus-Host Disease or an organ transplant failure resulting from graft rejection in an animal comprising the step of administering a pharmaceutical composition which comprises a therapeutically effective amount of an anti-TWEAK polypeptide monoclonal antibody and a pharmaceutically acceptable carrier. Because the Examiner acknowledges that applicant is in possession of the method recited in amended claim 1, the claims that depend from claim 1, *e.g.*, claims 4-5 and 12-14, should also be found allowable.

Claim 4, which depends from claim 1, has been amended to delete the dependency from cancelled claim 2, and recites that the animal is mammalian. Support for this claim may be found, *e.g.*, at page 5, line 18. Claim 5, which depends from claim 4, recites that the mammal is human. Support for this claim may be found, *e.g.*, at page 5, line 18. Claim 12, which depends from claim 1, has been amended to

recite that the Graft-versus-Host Disease or organ transplant failure is caused by a Th1 cell-mediated immune response. Claim 13, which depends from claim 1, has been amended to recite that the Graft-versus-Host Disease or organ transplant failure is caused by a Th2 cell-mediated immune response. Claim 14, which depends from claim 1, has been amended to recite that the Graft-versus-Host Disease or organ transplant failure is caused by a combination of a Th1 cell-mediated and a Th2 cell-mediated immune response. Support for claims 12-14 may be found, *e.g.*, at page 4, line 17-page 5, line 5; page 12, line 25-page 13, line 32; and page 15, lines 24-37.

Because applicant was clearly in possession of the inventions recited in instant claims 1, 4-5 and 12-14, applicant requests withdrawal of this rejection.

The rejection of claims 2-3 and 10-11 has been rendered moot by their cancellation herein.

CONCLUSIONS

For the foregoing reasons, applicant believes the claims are in condition for allowance and respectfully request that this application be passed to issue.

Respectfully submitted,

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Appendix of Amendments

1. (Amended) A method for blocking the development or treating or reducing the severity or effects of [an immunological disorder] a Graft-Versus-Host Disease or an organ transplant failure resulting from graft rejection in an animal comprising the step of administering a pharmaceutical composition which comprises a therapeutically effective amount of [a TWEAK blocking agent] an anti-TWEAK polypeptide monoclonal antibody and a pharmaceutically acceptable carrier.

4. (Amended) The method according to claim 1 [or 2], wherein the animal is mammalian.

12. (Amended) The method according to claim 1[2], wherein [the immune response] said Graft-Versus-Host Disease or said organ transplant failure is caused by a Th1 cell-mediated immune response.

13. (Amended) The method according to claim 1[2], wherein [the immune response] said Graft-Versus-Host Disease or said organ transplant failure is caused by a Th2 cell-mediated immune response.

14. (Amended) The method according to claim 1[2], wherein [the immune response includes both] said Graft-Versus-Host Disease or said organ transplant failure is caused by a combination of a Th1 and a Th2 cell-mediated immune response.